We claim:

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1. A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

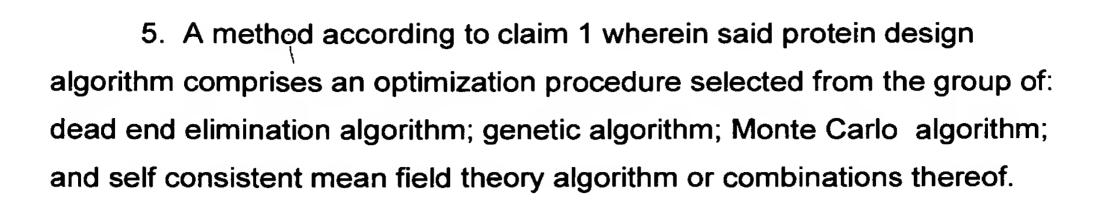
receiving at least one protein backbone structure;

applying a protein design algorithm to generate a protein sequence and structure;

sampling and evaluating one or more amino acids and rotamers within the context of said protein sequence and structure;

generating a probability matrix for said amino acids and rotamers that represent the viable sequence space for said protein backbone.

- A method according to claim 1 further comprising the step of: generating a single protein sequence from said probability matrix.
- 3. A method according to claim 1 further comprising the step of: generating a combinatorial library of proteins from said probability matrix.
- 4. A method according to claim 1 wherein said steps are repeated more than once to generate said probability matrix



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- 6. A method according to claim 1 wherein said protein backbone structure is taken from a natural protein.
- 7. A method according to claim 1 wherein said protein structure is generated by comparative modeling.
 - 8. A method according to claim 1 wherein the information from at least two probability matrices is combined to satisfy at least two constraints on sequence space.

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9. A method according to claim 1 wherein said protein backbone structure comprises an ensemble of related protein backbone structures.

10. A method according to claim 9 further comprising the step of:

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generating a single protein sequence from said probability matrix.

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generating a combinatorial library of proteins from said probability matrix

11. A method according to claim 9 further comprising the step of:

12. A method according to claim 9 wherein said steps are repeated more than once to generate said probability matrix.

13. A method according to claim 9 wherein said protein design algorithm comprises an optimization procedure selected from the group of: dead end elimination algorithm; genetic algorithm; Monte Carlo algorithm; and self consistent mean field theory algorithm or combinations thereof.

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14 A method according to claim 9 wherein said ensemble of related protein backbone structures are taken from a family of natural proteins.

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15. A method according to claim 9 wherein said ensemble of related backbone structures is derived from an NMR structure.

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16. A method according to claim 9 wherein said ensemble of related protein backbone structures is generated by a Monte Carlo simulation.

17. A method according to claim 9 wherein said ensemble of related protein backbone structures is generated by a molecular dynamics simulation.

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18. A method according to claim 9 wherein the information from at least two probability matrices is combined to satisfy at least two constraints on sequence space.

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19. A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

sampling and evaluating one or more amino acids and rotamers

receiving at least one complete protein sequence and structure;

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within the context of said	protein sec	quence and	structure;
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generating a probability matrix for said amino acids and rotamers that represent the viable sequence space for said protein backbone.

- 20. A method according to claim 19 wherein said protein sequence an structure is that of a natural protein.
- 21. A method according to claim 19 wherein said protein sequence and structure comprises an ensemble of related protein structures.
 - 22. A method according to claim 21 wherein said ensemble of proteins is generated by a Monte Carlo simulation.

23. A method according to claim 21 wherein said ensemble of proteins is generated by a molecular dynamics simulation .

- 24. A method according to claim 19 wherein said steps are repeated more than once to generate said probability matrix.
 - 25. A method according to claim 19 further comprising the step of : generating a single protein sequence from said probability matrix.
 - 26. A method according to claim 19 further comprising the step of:

 generating a combinatorial library of proteins from said

 probability matrix.

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- 27. A method according to claim 19 wherein said protein sequence and structure is generated by comparative modeling.
- 28. A method according to claim 19 wherein said protein sequence and structure is taken from a natural protein.
- 29. A method according to claim 19 wherein the information from at least two probability matrices is combined to satisfy at least two constraints on sequence space.
 - 30. A method for optimizing simulation or scoring function parameters that utilizes comparisons between designed sequences and natural sequences, comprising the steps of:

designing a protein sequence;

comparing said designed protein sequence to natural protein statistics;

modifying said simulation or scoring function parameters consistent with said comparison.

- 25 31. A method according to claim 30 wherein said steps are repeated at least once.
 - 32. A method according to claim 30 wherein said natural protein statistics are in the form of a position specific scoring matrix.
 - 33. A method according to claim 30 wherein said natural protein

statistics are in the form of amino acid composition

34. A method for optimizing simulation or scoring function parameters that utilizes comparisons between designed sequences and natural sequences, comprising the steps of:

calculating an amino acid probability matrix;

comparing said matrix to natural protein statistics;

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modifying simulation or scoring function parameters consistent with said comparison.

- 35. A method according to claim 34 wherein the sequence of steps is repeated at least once.
 - 36. A method according to claim 34 wherein said natural sequence statistics are in the form of a position specific scoring matrix.
- 37. A method according to claim 34 wherein said natural sequence statistics are in the form of amino acid composition.